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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/816,467	03/26/2001	Laurent Coen	3495.0174-01	7062

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EXAMINER	
CHEN, SHIN LIN	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 12/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/816,467	COEN ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17,18,21-23,34 and 35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17,18,21-23,34 and 35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

In response to the "Decision on Appeal" mailed 10-26-05, the finality of the Official action mailed 6-4-03 has been withdrawn. In view of a new art rejection, an action on merit follows.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claim 22 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The terms "SMN", "NT-3", "NT-4/5", "CRE" and "ICE" in claim 22 are vague and renders the claim indefinite. These terms are abbreviations and can stand for various meanings. Spelling out the terms at the first occurrence would be remedial.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 17 and 21 are rejected under 35 U.S.C. 102(b) as being anticipated by Fairweather et al., 1995 (US Patent 5,443,966).

Claims 17 and 21 are directed to a hybrid fragment of tetanus toxin comprising fragment C and fragment B or a fraction of fragment B having at least 11 amino acid residues, wherein the hybrid fragment is capable of transferring in vivo a protein, a peptide, or a polynucleotide through a neuromuscular junction and at least one synapse, and a composition comprising an active molecule in association with said hybrid fragment.

Fairweather teaches construction of expression plasmid pTet18 expressing a polypeptide which comprises 121 residues of B fragment and all 451 carboxy-terminal residues of C fragment of tetanus toxin, transfection of E. coli cells with said expression plasmid, and culturing of the transfected E. coli cells. Fairweather assays expressed tetanus hybrid protein by SDS-PAGE gel and Western blotting using rabbit anti-C fragment sera (e.g. column 8). Since the specification fails to specifically define the term "active molecule", therefore, the solution containing the expressed tetanus hybrid protein during the assay is considered an active molecule. Further, claims 17 and 21 are product claims and Fairweather teaches every limitation of the claimed product. Thus, it is inherent that the tetanus hybrid protein taught by Fairweather has the ability to transfer in vivo a protein, a peptide, or a polynucleotide through a neuromuscular junction and at least one synapse. Therefore, claims 17 and 21 are anticipated by Fairweather.

5. Claims 17 and 21 are rejected under 35 U.S.C. 102(a) as being anticipated by Fishman et al., 1996 (Society for Neuroscience Abstracts, Vol. 22, No. 1-3, pp. 1705).

Claims 17 and 21 are directed to a hybrid fragment of tetanus toxin comprising fragment C and fragment B or a fraction of fragment B having at least 11 amino acid residues, wherein the hybrid fragment is capable of transferring in vivo a protein, a peptide, or a polynucleotide through a neuromuscular junction and at least one synapse, and a composition comprising an active molecule in association with said hybrid fragment.

Fishman teaches that C-fragment of tetanus toxin (CF) has been studied as a carrier for delivery of therapeutic proteins to neurons. Fishman compares full-length tetanus toxin (TTX) and CF in its capacity to bind and be internalized by neurons by ELISA and shows that TTX is superior to its ganglioside binding fragment CF in the capacity for neuronal binding and internalization. Fishman suggests atoxic tetanus proteins containing additional molecular domains as well as CF may be more suitable vectors for linkage with therapeutic proteins and delivery to neurons. Since the specification fails to specifically define the term "active molecule", therefore, the solution containing the TTX is considered an active molecule. Further, the claimed hybrid fragment of tetanus toxin encompasses full-length tetanus toxin protein. Thus, claims 17 and 21 are anticipated by Fishman.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 17, 18, 21, 23, 34 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fishman et al., 1996 (Society for Neuroscience Abstracts, Vol. 22, No. 1-3, pp. 1705) in view of Mueller, 1994 (Report, ARO-27890.1-LS, Order No. AD-A290 501, NTIS, p. 1-15) and Hohne-Zell et al., 1993 (FEBS Letters, Vol. 336, No. 1, p. 175-180).

Claims 17, 18, 21, 23, 34 and 35 are directed to a hybrid fragment of tetanus toxin comprising fragment C and fragment B or a fraction of fragment B having at least 11 amino acid residues or further containing fragment A devoid of its zinc-binding motif, wherein the hybrid fragment is capable of transferring in vivo a protein, a peptide, or a polynucleotide through a neuromuscular junction and at least one synapse, and a composition comprising an active molecule in association with said hybrid fragment. Claims 23, 34 and 35 specify the active molecule is a polynucleotide encoding a protein and said polynucleotide further comprises a promoter capable of expression in neurons or further comprises an enhancer.

Fishman teaches that C-fragment of tetanus toxin (CF) has been studied as a carrier for delivery of therapeutic proteins to neurons. Fishman compares full-length tetanus toxin (TTX) and CF in its capacity to bind and be internalized by neurons by ELISA and shows that TTX is

superior to its ganglioside binding fragment CF in the capacity for neuronal binding and internalization. Fishman suggests atoxic tetanus proteins containing additional molecular domains as well as CF may be more suitable vectors for linkage with therapeutic proteins and delivery to neurons (last 4 lines).

Fishman does not teach a hybrid fragment of tetanus toxin in association with a polynucleotide under the control of a promoter and/or an enhancer. Fishman also does not specifically teach a hybrid fragment further comprising a fraction of a fragment A devoid of its toxic activity corresponding to zinc-binding motif between amino acid residues 225 and 245.

Mueller teaches that tetanus toxin is specific for uptake into neurons and carboxy terminal (C-fragment) of the protein alone is not toxic and is sufficient for internalization and transport (retrograde) as a carrier molecule for neuron specific gene transfer in vivo, and the foreign gene can be specifically controlled by the gene's promoter. The toxic portion of the protein resides in the amino terminal (e.g. p. 3 and 4). The non-toxic portion of tetanus toxin (C fragment) can be covalently attached to polylysine whose positive charge serves as a bridge to the non-covalent, electrostatic binding of the negatively charged DNA (e.g. p. 4). Mueller lists neuronal cells that can be used for gene delivery in vitro (see Table 1). Mueller also teaches using RSV promoter for neuron-specific expression of beta-galactosidase (e.g. p. 9).

Hohne-Zell teaches zinc and the putative zinc-binding domain constitute the active site of the tetanus toxin light chain and replacement of histidine (position 233) by cysteine or valine and of glutamate (position 234) by glutamine completely abolished the activity of light chain on calcium induced catecholamine release (e.g. abstract).

It would have been obvious for one of ordinary skill at the time of the invention to generate claimed hybrid fragment or composition because modifying the composition of Fishman et al. by replacing the polypeptide with a larger fragment of tetanus toxin (in addition to C fragment) was better in delivering a molecule to neurons and also because C-fragment of the tetanus toxin alone is not toxic and the toxic portion of the protein resides in the amino terminal, and in combination with the teaching of Hohne-Zell that the putative zinc-binding domain constitutes the active site of the tetanus toxin light chain would make it obvious for one of ordinary skill to remove said zinc-binding domain when generating a tetanus toxin fragment for neuron specific transport. It also would have been obvious for one of ordinary skill at the time of the invention to associate the tetanus protein as taught by Fishman with a polynucleotide because Fishman teaches that atoxic tetanus proteins containing additional molecular domains as well as CF may be more suitable vectors for linkage with therapeutic proteins and delivery to neurons, and Mueller teaches that the tetanus C-fragment can be used to complex with DNA for neuron specific gene transfer in vivo and use of RSV promoter for said gene transfer.

One ordinary skill at the time the invention was made would have been motivated to do so in order to generate a tetanus hybrid protein capable of retrograde transport as a carrier molecule for neuron specific gene transfer in vivo as taught by Mueller and Fishman with reasonable expectation of success.

9. Claims 17, 21 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fishman et al., 1996 (Society for Neuroscience Abstracts, Vol. 22, No. 1-3, pp. 1705) in view of

Khan et al., 1995 (WO 95/04151) and Mueller, 1994 (Report, ARO-27890.1-LS, Order No. AD-A290 501, NTIS, p. 1-15).

Claims 17, 21 and 22 are directed to a hybrid fragment of tetanus toxin comprising fragment C and fragment B or a fraction of fragment B having at least 11 amino acid residues, wherein the hybrid fragment is capable of transferring in vivo a protein, a peptide, or a polynucleotide through a neuromuscular junction and at least one synapse, and a composition comprising an active molecule in association with said hybrid fragment. Claim 22 specifies the active molecule is a protein as recited.

Fishman teaches that C-fragment of tetanus toxin (CF) has been studied as a carrier for delivery of therapeutic proteins to neurons. Fishman compares full-length tetanus toxin (TTX) and CF in its capacity to bind and be internalized by neurons by ELISA and shows that TTX is superior to its ganglioside binding fragment CF in the capacity for neuronal binding and internalization. Fishman suggests atoxic tetanus proteins containing additional molecular domains as well as CF may be more suitable vectors for linkage with therapeutic proteins and delivery to neurons (last 4 lines).

Fishman does not specifically teach association of the recited proteins with the claimed hybrid fragment of tetanus toxin.

Khan teaches construction of a DNA construct comprising a DNA sequence encoding a fusion protein of the formula: TetC-(Z)a-Het, wherein the TetC is the C fragment of tetanus toxin and Het is a heterozygous protein (e.g. abstract). Khan teaches using the DNA construct in producing a fusion protein and the use of said fusion protein as a vaccine (e.g. p. 4).

Mueller teaches that tetanus toxin is specific for uptake into neurons and carboxy terminal (C-fragment) of the protein alone is not toxic and is sufficient for internalization and transport (retrograde) as a carrier molecule for neuron specific gene transfer in vivo. The non-toxic portion of tetanus toxin (C fragment) can be covalently attached to polylysine whose positive charge serves as a bridge to the non-covalent, electrostatic binding of the negatively charged DNA (e.g. p. 4). Mueller lists neuronal cells that can be used for gene delivery in vitro (see Table 1). Mueller also teaches using RSV promoter for neuron-specific expression of beta-galactosidase (e.g. p. 9).

It would have been obvious for one of ordinary skill in the art at the time of the invention to associate the recited proteins in claim 22 with the claimed hybrid fragment of tetanus toxin because Fishman suggests atoxic tetanus proteins containing additional molecular domains as well as CF may be more suitable vectors for linkage with therapeutic proteins and delivery to neurons and Khan teaches association of the C fragment of tetanus toxin with any heterozygous protein, and further, most of the proteins recited in claim 22 are expressed in neurons and Mueller teaches using the C-fragment as a carrier molecule for neuron specific gene transfer.

One having ordinary skill in the art at the time the invention was made would have been motivated to do so in order to deliver the protein as a vaccine as taught by Khan or deliver the therapeutic protein to neurons as taught by Mueller and Fishman with reasonable expectation of success.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for this group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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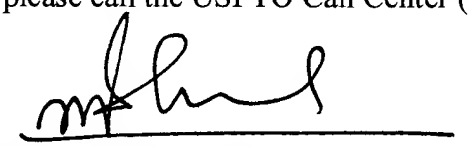

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